In Vivo Generation of Engraftable Murine Hematopoietic Stem Cells by Gfi1b, c-Fos, and Gata2 Overexpression within Teratoma.

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Public Summary:
Blood or hematopoietic stem cells are necessary for successful bone marrow transplantation, which is a curative therapy for a range of blood diseases. However, blood stem cells are rare and difficult to expand in a culture dish, limiting the availability of this important cell type for transplantation. Here, we investigated in vivo transdifferentiation as a way to generate functional HSCs from iPSCs, which represent an unlimited cell source in regenerative medicine. We found that expression of three transcription factors (Gfi1b, c-Fos, Gata2) could generate functional HSCs from iPSCs in vivo. This transcription factor combination had previously been shown to generate blood cells in vitro, but wasn't sufficient to generate blood stem cells. Our findings highlight the importance of the cellular niche or microenvironment for blood stem cell formation from iPSCs.

Scientific Abstract:
Generation of hematopoietic stem cells (HSCs) from pluripotent stem cells (PSCs) could potentially provide unlimited HSCs for clinical transplantation, a curative treatment for numerous blood diseases. However, to date, bona fide HSC generation has been largely unsuccessful in vitro. We have previously described proof of concept for in vivo HSC generation from PSCs via teratoma formation. However, our first-generation system was complex and the output low. Here, we further optimize this technology and demonstrate the following: (1) simplified HSC generation using transcription factor overexpression; (2) improved HSC output using c-Kit-deficient host mice, and (3) that teratomas can be transplanted and cryopreserved. We demonstrate that overexpression of Gfi1b, c-Fos, and Gata2, previously reported to transdifferentiate fibroblasts into hematopoietic progenitors in vitro, can induce long-term HSC formation in vivo. Our in vivo system provides a useful platform to investigate new strategies and re-evaluate existing strategies to generate HSCs and study HSC development.